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GUEST EDITORIAL

Case Against Axillary Lymphadenectomy for Most Patients With Infiltrating Breast Cancer

BLAKE CADY, MD*
Department of Surgical Oncology, Harvard Medical School, Boston, Massachusetts

The data from randomized prospective control trials of breast cancer treatment show, incontrovertibly, that lymph node metastases in breast cancer are ''indicators but not governors'' [1] of survival. A similar general principle applies to lymph node metastases in all human solid tumors. In prospective trials of all other organ sites where a varying extent of lymphatic dissection is compared, the survival is equivalent—melanoma [2], colon cancer [3], gastric cancer [4], lung cancer [5]. In breast cancer this truism applies to internal mammary node dissection [6], supraclavicular node dissection [7], and the extent of axillary dissection [8]. Although it is true that removing palpable axillary adenopathy serves a therapeutic benefit in ridding the patient of a definable mass, prophylatic dissection in clinically negative axillas provides no inherent therapeutic benefit since there is no grossly apparent disease in the axillary lymph nodes, and the treatment serves only as a method of selection of adjuvant systemic therapy.

The possibility of long-term survival of patients who have positive lymph nodes is well established and is related to the extent of axillary nodal disease. Thus, Harvey and Auchincloss [9] in 1968 demonstrated that not only in breast cancer, but also in colon, rectal, and lung cancer, <4% of 5-year survivors had five or more positive nodes. More than 70% of survivors with those various cancers had negative nodes at the original surgery.

There is a physiological explanation why patients who have lymph node metastases may not develop other metastatic disease. This involves the demonstration of ''lymph node'' only, organ-specific, metastatic cells [10], just as there can be ''liver only'' [1] or ''lung only'' [2] cells in colorectal carcinoma or sarcoma, respectively. In these human model systems, despite distant metastases in liver or lung, long-term cures after resection of metastases are achievable because of the organ specificity of certain clones of cells. Similarly, organ-specific lymph node metastatic cells can be demonstrated that do not have the capacity, apparently, to lodge or grow in other organ sites [13,14]. This biological behavior of metastatic cells, well substantiated by animal experiments [15,16], provides the explanation why patients with lymph node metastases may yet be curable even without removal of the lymph nodes and why lymph node metastases are ''indicators but not governors'' [1] of survival.

The astonishing decreases in size and lymph node positivity in modern invasive breast cancer presentation resulting from mammographic screening of increasing proportions of women in the United States is well documented [17]. Thus the proportion of ''positive'' axillas at the New England Deaconess Hospital in the years 1989 through 1993 was only 31% utilizing lymph node dissections and the traditional histologic examination that was consistent throughout the 65 years of the Pathology Department [17]. Numerous contemporary articles describe very low rates of lymph node metastases in T_{1a} and T_{1b} invasive breast cancers [18], generally ~5% in T_{1a} [19,20] and 10% in T_{1b} [18–20]. Although this low incidence is not uniformly accepted and the American College of Surgeons survey shows strikingly higher rates [21], there is acceptance of the general assumption that a decreasing incidence of node metastases is associated with decreasing size and that ductal carcinoma in situ with micro invasion has only a 1% or 2% risk of nodal metastases [22]. The re-examination of ''negative'' axillary dissection specimens, or the routine use of histochemical markers, or multiple sections of the axillary lymph nodes can reveal unsuspected metastatic nodal disease, but these are usually micrometastases [23]. The implication of such micrometastases in prognosis is debatable, as many articles indicate no decrement in survival with such incidentally discovered micrometastases

*Correspondence to: Blake Cady, M.D., Department of Surgical Oncology, Harvard Medical School, New England Deaconess Hospital, 110 Francis Street 2-H, Boston, MA 02215. Fax: 617-632-7433.
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TABLE I. Invasive Breast Cancer Cost: Benefit Analysis of Axillary Dissection

Pro:	Fulfills pathologic staging requirement.
	Enables judgements regarding adjuvant therapy
Con:	30% of 1990s patients have Mgm ⩽1 cm cancer.
	: <10% rate of axillary metastases.
	40% of 1990s patients have 1° cancer features that suggest adjuvant therapy even if nodes negative.
	15% have clinical arm edema postoperatively.
	General anesthesia, short hospital stay, surgeons and anesthesia fee = $10,000 per dissection.
	No therapeutic benefit.

TABLE II. Primary Invasive Breast Cancer <10 mm (T_{1a} & T_{1b})*

	Adjuvant Rx	10 year Survival rate	10 year Survival
Scenario A			
100 patients: No axilla			
90 − Nodes	No	90%	81 pts
10 + Nodes	No	70%	7 pts
			88 pts
100 patients: Axillary dissection			
90 − Nodes	No	90%	81 pts
10 + Nodes	Yes	80%	8 pts
			89 pts
Scenario B			
100 patients: No axilla			
90 − Nodes	No	80%	72 pts
10 + Nodes	No	55%	6 pts
			78 pts
100 patients: Axillary dissection			
90 − Nodes	No	80%	72 pts
10 + Nodes	Yes	70%	7 pts
			79 pts

*Assume: 10% incidence + nodes axilla; 33% reduction in recurrence with adjuvant Rx.

[24] as there are ones demonstrating that there is a worse prognosis [25]. At the present time this issue awaits further clarification. It is important that we develop standardized procedures for axillary nodal pathological examination in order to make any sense out of the variety of literature descriptions of ''positive'' nodal examinations and to achieve any kind of comparisons between reports from different institutions [26].

A cost-benefit analysis of the use of axillary dissections where the expected incidence of positive nodes is 10% or less indicates that for each life saved at 10 years, the cost will be over $1,000,000, an unsupportable medical expense according to health planners examining cost-benefit ratios, [Table I, Table II]. Indeed, such a cost is a minimal figure since three-quarters of breast cancer patients are post menopausal and adjuvant therapy with Tamoxifen is far less effective compared to chemotherapy (15% vs. 33% proportional reduction in recurrence) [27]. The one life saved for $1,000,000 results from the assumed 33% reduction in mortality demonstrated in premenopausal women, who constitute only 25% of invasive breast cancer cases. If the proportional reduction in recurrence and mortality is much less than the assumed 33%, as is found in adjuvant with Tamoxifen (15%), the cost would be more than $2,000,000 per life saved at 10 years, clearly an unsupportable medical expense. These assumptions are based on axillary dissections done under general anesthesia in the hospital with a very short stay at a total cost of ~$10,000 each.

Recently, a new technique of ''sentinel'' axillary lymph node biopsy, utilizing either vital dyes or radionuclide markers, allows a physiologically representative node from the regional node basin to be removed under local anesthesia [28,29]. Studies so far indicate that this physiologically defined entrance to the regional node basin can be identified in >90% of cases with nearly a 100% accuracy in terms of predicting lymph node positivity [28,29]. Such a physiologically defined sampling of an axillary lymph node may be all that is required for selecting adjuvant therapy since the exact number of lymph nodes is not of proven benefit in selecting adjuvant therapy. Indeed, it makes no sense to utilize different therapy for patients with multiple node metastases in contrast to one or two metastases if the goal is to maximize effective therapy. In that case, any patient with a positive node should get maximal adjuvant therapy once it has been proven to be the most beneficial. Medical oncologists routinely advocate dose escalation to maximize effectiveness and claim that toxicity can be minimized. Thus the only critical decision for adjuvant therapy selection is whether lymph nodes are positive or negative, not the exact number of lymph node metastases. In practical human terms, most patients do not need to know, nor can they comprehend or manage different changes in lifestyle, from subtle differences in prognostic implication of the variation between two nodes or six node metastases, for instance. From a patient point of view, only the need to select adjuvant therapy to reduce potential recurrence is truly useful information. If some time in the future bone marrow transplantation or stem cell rescue from superlethal chemotherapy can be proven more effective in a randomized trial, then an argument could be made for actually dissecting only those axillas proven to be positive by an initial sentinel node biopsy for actual counting of numbers of positive nodes. However, such selection of carefully defined patients will not constitute a major group in breast cancer with the increasing use of screening mammography.

The increasing acceptance of induction chemotherapy treatment of advanced primary breast cancer with clinical estimation of response for prognostication and therapy selection will eliminate this group of patients from the need for axillary dissection [30]. In advanced primary breast cancer, axillary lymph nodes should deliberately

not be dissected since they need to be observed for estimation of clinical response. Utilizing this approach, numerous authors [30–32] have demonstrated major improvements in long-term outcome and breast preservation with advanced primary or inflammatory breast cancer. Since the clinical response of gross disease is the key prognostic feature in such patients, all manifestations of the advanced primary disease, such as palpable axillary lymph nodes or primary cancer, needs to be left intact.

We are rapidly entering an era when routine axillary dissection in all cases of breast cancer will cease. By the year 2000, only a small minority of invasive breast cancer patients will need or benefit from axillary node dissection. This can be predicted not only because physiologically and biologically lymph node metastases are ''indicators nor governors'' of outcome, but because the incidence of lymph node metastases is decreasing so rapidly with population mammographic screening. Eventually we will have to resort to primary cancer features to select adjuvant therapy as node metastases become uncommon [33,34]. In addition, the technique for reliably sampling the regional nodes by the use of physiologically defined ''sentinel'' lymph node biopsy under local anesthesia will provide whatever nodal information is critical.

This is truly a ''new era'' in breast cancer [17] related to the rapid improvement in clinical staging from population screening. Thus our catalogue of traditional arguments for the need for axillary dissection will rapidly be outdated in favor of a practical test of primary tumor features to predict prognosis with increasing accuracy, regardless of lymph node status. More and more patients with negative axillary lymph nodes will be treated with adjuvant therapy because of poor prognostic primary tumor features. This honors traditional teaching that ''if the results of a test don't change what you do, don't do the test'' and recognizes that axillary dissection in a clinically negative axilla is a test, not a therapy.

Even in 1996, it can be demonstrated that an axillary dissection can be justified in only ~25% of patients if one considers: (1) the high proportion of T_{1a} or T_{1b} cancers that have only a 10% or lower lymph node positive rate [17,28], (2) the 40% of patients who have primary tumor features that can be utilized to select adjuvant therapy regardless of the status of lymph nodes, and (3) the 5% or 10% of patients who present with advanced primary disease justifying induction chemotherapy.

Figure 1 is an algorithm for the selection of patients who might benefit from axillary dissections in 1996. By the year 2000, however, the proportion of patients requiring axillary dissection to obtain nodal pathology to give refined prognostic information will be very low. Only a few patients will need complete axillary dissection to select accurately the best available therapy on the basis of the number of nodal metastases, since sentinel

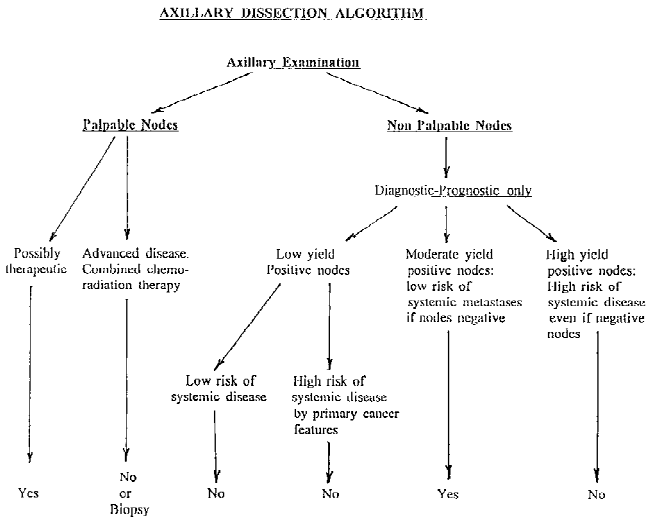

Fig. 1. Algorithm for the selection of patients who might benefit from axillary dissections.

node biopsy can provide the initial axillary nodal pathology. Axillary dissection could be limited only to those patients who have a positive sentinel node if the exact number of axillary nodes is required for entrance into research or clinical protocols. However, if the sentinel node shows only a micrometastases, nothing further need be contemplated for therapy either in the axilla or systemically since the prognosis of such patients is essentially that of patients with negative nodes. Therapeutic axillary dissection for recurrent or persistent disease still will be required on occasion, however.

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